Journal of Nuclear Medicine, published on April 14, 2022 as doi:10.2967/jnumed.122.263790

Cost-effectiveness of ^{18}F-FET PET for early treatment response assessment in glioma patients following adjuvant temozolomide chemotherapy

Jurij Rosen[1], Garry Ceccon[1], Elena K. Bauer[1], Jan-Michael Werner[1], Caroline Tscherpel[1], Veronika Dunkl[1], Marion Rapp[2,3], Michael Sabel[2,3], Ulrich Herrlinger[3,4], Alexander Heinzel[5,6], Niklas Schäfer[3,4], Maximilian Ruge[3,7], Roland Goldbrunner[3,8], Gabriele Stoffels[5], Christoph Kabbasch[9], Gereon R. Fink[1,5], Karl-Josef Langen[3,5,6], and Norbert Galldiks[1,3,5]

[1]Dept. of Neurology, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany

[2]Dept. of Neurosurgery, University Hospital Duesseldorf, Duesseldorf, Germany

[3]Center for Integrated Oncology (CIO), Universities of Aachen, Bonn, Cologne, and Düsseldorf, Germany

[4]Division of Clinical Neuro-Oncology, Department of Neurology, University of Bonn Medical Center, Bonn, Germany

[5]Institute of Neuroscience and Medicine (INM-3, -4), Research Center Juelich, Juelich, Germany

[6]Dept. of Nuclear Medicine, University Hospital Aachen, Aachen, Germany

[7]Dept. of Stereotaxy and Functional Neurosurgery, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany

[8]Dept. of General Neurosurgery, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany

[9]Dept. of Neuroradiology, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany

Running title: Cost-effectiveness of ^{18}F-FET PET

Corresponding author

Norbert Galldiks, MD
Inst. of Neuroscience and Medicine (INM-3), Research Center Juelich, Leo-Brandt-St. 5, 52425 Juelich, Germany
Phone: +49-2461-61-5914, FAX: +49-2461-61-1518
Email: n.galldiks@fz-juelich.de

and Dept. of Neurology, University Hospital Cologne, Kerpener St. 62, 50937 Cologne, Germany
Phone: +49-221-478-86124, FAX: +49-221-478-5669
Email: norbert.galldiks@uk-koeln.de

First author

Jurij Rosen, MD (resident)
Dept. of Neurology, University Hospital Cologne, Kerpener St. 62, 50937 Cologne, Germany
Phone: +49-221-478-4015, FAX: +49-221-478-5669
Email: jurij.rosen@uk-koeln.de

Word count: 4314

ABSTRACT

Rationale: In light of increasing healthcare costs, higher medical expenses should be justified socio-economically. Therefore, we calculated the effectiveness and cost-effectiveness of positron emission tomography (PET) using the radiolabeled amino acid O-(2-[^{18}F]-fluoroethyl)-L-tyrosine (^{18}F-FET) compared to conventional magnetic resonance imaging (MRI) for early identification of responders to adjuvant temozolomide chemotherapy. A recently published study in isocitrate dehydrogenase-wildtype glioma patients suggested that ^{18}F-FET PET parameter changes predicted a significantly longer survival already after two cycles while MRI changes were not significant.

Methods: To determine the effectiveness and cost-effectiveness of serial ^{18}F-FET PET imaging, we analyzed published clinical data and calculated the associated costs from the perspective of the German Statutory Health Insurance system. Based on a decision-tree model, the effectiveness of ^{18}F-FET PET and MRI was calculated, i.e., the probability to correctly identify a responder as defined by an overall survival ≥15 months. To determine the cost-effectiveness, the incremental cost-effectiveness ratio (ICER) was calculated, i.e., the cost for each additionally identified responder by ^{18}F-FET PET who would have remained undetected by MRI. The robustness of the results was tested by deterministic and probabilistic Monte Carlo sensitivity analyses.

Results: Compared to MRI, ^{18}F-FET PET increased the rate of correctly identified responders to chemotherapy by 26%; thus, four patients needed to be examined by ^{18}F-FET PET to identify one additional responder. Considering the respective cost for serial ^{18}F-FET PET and MRI, the ICER resulted in €4,396.83 for each additional correctly

identified responder by ^{18}F-FET PET. Sensitivity analyses confirmed the robustness of the results.

Conclusion: In contrast to conventional MRI, the model suggests that ^{18}F-FET PET is cost-effective in terms of ICER values. Considering the high cost of temozolomide, the integration of ^{18}F-FET PET has the potential to avoid premature chemotherapy discontinuation at reasonable cost.

KEYWORDS

economic evaluation; treatment monitoring, treatment-related changes; tumor-to-brain ratio; amino acid PET

INTRODUCTION

Glioblastomas represent a pheno- and genotypically defined group of brain tumors characterized by a rapid and infiltrative growth resulting in a dismal prognosis for affected patients (*1*). Standard of care consists of resection, followed by radiotherapy with concomitant and adjuvant temozolomide chemotherapy, according to the EORTC-NCIC 22981/26981 trial (*2*). To evaluate treatment effects, contrast-enhanced anatomical magnetic resonance imaging (MRI) is the most widely used tool to assess response to chemoradiation and adjuvant chemotherapy. However, standard contrast-enhanced MRI provides an insufficient diagnostic performance for identifying treatment-related changes such as pseudoprogression (*3-8*), with an accuracy of approximately 50% (*3*). For example, MRI signal changes (e.g., an increase of the extent of contrast enhancement, newly diagnosed contrast-enhancing lesions, or an increase of signal alterations on fluid-attenuated inversion recovery (FLAIR) sequences) may be related to infection or neuroinflammation, ischemia, demyelination, or treatment-related effects, e.g., related to radiotherapy or chemoradiation with alkylating agents. All these changes may be difficult to distinguish from actual tumor progression and impact patient care.

Several studies have indicated that the assessment of the metabolic tumor activity by positron emission tomography (PET) using the radiolabeled amino acid *O*-(2-[^{18}F]fluoroethyl)-L-tyrosine (^{18}F-FET) is both helpful and superior to conventional MRI for the detection of treatment-related changes following chemoradiation with temozolomide in glioma patients (*3,9,10*). In addition, a recent study by Ceccon et al. (*11*) investigated the value of serial ^{18}F-FET PET in glioma patients for early assessment of treatment response to adjuvant chemotherapy with temozolomide. In that study, 41 newly diagnosed

glioma patients after resection or biopsy and chemoradiation with temozolomide underwent ^{18}F-FET PET imaging before initiation (baseline) of adjuvant chemotherapy with temozolomide and after the second cycle (follow-up). The authors concluded that, in contrast to MRI, a metabolic decrease of static ^{18}F-FET PET parameters from baseline to follow-up significantly predicted both a prolonged progression-free survival (PFS) and overall survival (OS), thus allowing identification of responders to adjuvant temozolomide early after treatment initiation.

Nevertheless, the integration of ^{18}F-FET PET in the care of glioma patients is associated with additional costs that have to be weighed against relevant clinical benefits for affected patients. In recent years, only a few studies have addressed the topic of cost-effectiveness of ^{18}F-FET PET in the care of glioma patients, which contrasts the considerable evidence confirming its usefulness. In detail, ^{18}F-FET PET has already been proven to be cost-effective for surgical target selection (*12,13*), and for the response assessment of radiotherapy with concomitant temozolomide (*14*) or bevacizumab (*15*) in glioma patients.

Considering the diagnostic improvements and additional costs of ^{18}F-FET PET compared to conventional MRI, the already published data of Ceccon et al. (*11*) were evaluated regarding the effectiveness of serial ^{18}F-FET PET scans to identify responders to adjuvant temozolomide chemotherapy and cost-effectiveness. This analysis was performed from the perspective of the Statutory Health Insurance system in Germany. To the best of our knowledge, this is the first study investigating the effectiveness and cost-

effectiveness of serial ^{18}F-FET PET imaging in the care of glioma patients following adjuvant chemotherapy with temozolomide.

PATIENTS AND METHODS

Input Data

The clinical value of ^{18}F-FET PET compared to conventional MRI for identifying responders to adjuvant temozolomide chemotherapy was published by Ceccon and colleagues (*11*). In that study, 41 adult patients (mean age, 52 ± 13 years) with newly diagnosed and histomolecularly characterized glioma (glioblastoma, 90%) were included. The institutional review board had approved this study and all subjects signed a written informed consent for their participation in the study and evaluation of their data for scientific purposes. After resection or stereotactic biopsy, all patients completed radiotherapy (60 Gy) with concomitant and adjuvant temozolomide chemotherapy over 6 cycles according to the EORTC/NCIC 22981/26981 trial (*2*). After chemoradiation, all patients underwent both ^{18}F-FET PET and MRI within 7 days before adjuvant temozolomide initiation and after the second cycle of adjuvant temozolomide. MRI changes at first follow-up compared to baseline were assigned according to the Response Assessment in Neuro-Oncology (RANO) criteria (*16*). For the evaluation of imaging data, static ^{18}F-FET PET parameters such as tumor-to-brain ratios (TBR) and metabolic tumor volumes were calculated (*17*). The authors concluded that MRI changes (according to RANO criteria) did not have any predictive value for the PFS and OS. In contrast, a change of static ^{18}F-FET PET biomarkers such as the maximum TBR and the metabolic tumor volume from baseline to follow-up predicted a significantly longer PFS and OS, thus

enabling ^{18}F-FET PET imaging to early identify responders and non-responders to adjuvant temozolomide chemotherapy.

Decision-tree Model for Comparison of the Effectiveness

A decision-tree model was developed to compare the effectiveness of ^{18}F-FET PET and MRI, i.e., the probability of correctly identifying a responder. As described previously (*12-14,18*), this model was constructed: patients were divided into responders and non-responders depending on individual neuroimaging findings on ^{18}F-FET PET and MRI (Figure 1). Chance node one (N1) indicated the probability of a patient being a responder or a non-responder according to TBR_{max} changes. Chance node two (N2) indicated this probability concerning MRI changes according to RANO criteria. The subsequent chance nodes N3-6 assigned each of the four groups of PET and MRI responders and non-responders to the patients' outcomes. In the study by Ceccon et al. (*11*), the response was associated with a PFS ≥ 9 months and an OS ≥ 15 months. We defined the probability of correct identification of a responder to adjuvant chemotherapy with temozolomide as the primary outcome of our model.

Cost Calculation

The costs were calculated from the perspective of the German Statutory Health Insurance system. As the German statutory health insurance usually does not cover ^{18}F-FET PET costs in the care of glioma patients, the costs for both ^{18}F-FET PET and conventional MR imaging were calculated on the basis of the "Medical Fee Schedule for Care Outside the Statutory Health Insurance Scheme" (http://www.e-bis.de/goae/defaultFrame.htm) to provide an equal and consistent comparison of the cost.

The costs taken into consideration for ^{18}F-FET PET were as follows (procedure's index number in parenthesis): patient consultation €10.72 (1), report on diagnostic findings €17.43 (75), intravenous injection €9.38 (253), scintigraphy of the brain €125.91 (5430), PET with quantitative analysis €786.89 (5489), and tracer production costs of €616.

For MRI, the costs were as follows: patient consultation €10.72 (1), physical examination €10.72 (5), report on diagnostic findings €17.43 (75), high-pressure intravenous injection €40.23 (346), surcharge for perfusion imaging €75.19 (3051), MRI with three-dimensional and apparent diffusion coefficient (ADC) reconstruction requiring substantial technical effort €641.16 (5700), additional MRI series with three-dimensional and ADC reconstruction requiring substantial technical effort €145.72 (5731), and surcharge for computer analysis €46.63 (5733).

Thus, the neuroimaging cost for one ^{18}F-FET PET was estimated at €1,566.33 and €987.80 for one MRI scan. As the assessment of response comprised two scans, the total costs for each patient resulted in €3,132.66 for ^{18}F-FET PET and €1,975.60 for MRI.

Overall cost of concomitant radiochemotherapy followed by six cycles of temozolomide is approximately €30,000 (*19,20*).

Cost-Effectiveness

The difference in cost between two serial ^{18}F-FET PET and MRI scans divided by the incremental effectiveness (IE) to correctly detect a responder to adjuvant chemotherapy with temozolomide resulted in the incremental cost-effectiveness ratio (ICER):

$$\mathrm{ICER} = \frac{\mathrm{Cost}\ (18\mathrm{F} - \mathrm{FET}\ \ \mathrm{PET}) - \mathrm{Cost}\ (\mathrm{MRI})}{\mathrm{Effectiveness}\ (18\mathrm{F} - \mathrm{FET\ PET}) - \mathrm{Effectiveness}\ (\mathrm{MRI})}$$

Sensitivity Analyses

Deterministic and probabilistic sensitivity analyses were performed to test the robustness of the calculated effectiveness.

In particular, the deterministic sensitivity analysis evaluated the impact of each independent variable (N1-6) on the resulting ICER. For this, we used confidence intervals already applied in previous studies, which evaluated the cost-effectiveness of ^{18}F-FET PET in glioma patients undergoing chemoradiation with concomitant temozolomide (*14*) or antiangiogenic therapy using bevacizumab (*15*) (Table 1).

For probabilistic sensitivity analysis, a Monte Carlo simulation was performed using 10,000 sets of random values for the independent variables (N1-6). The distribution of these random values was defined by the mean of our decision-tree and the standard deviation (SD), which was set according to the respective confidence interval of the deterministic sensitivity analysis, similar to Baguet et al. (*14*) (Table 2).

For each set of random values, we determined the IE and ICER. Moreover, ^{18}F-FET PET and MRI costs were modeled by a gamma distribution with the mean of the difference in cost between serial ^{18}F-FET PET and MRI scans and an SD of 50%. Results from the probabilistic sensitivity analysis for effectiveness values were displayed by mean, median, SD, 95% confidence interval (CI), minimum and maximum values, and the 2.5%-, 10%-, 90%-, 97.5%-percentiles. All calculations, figures, and simulations were performed using the R software (*21*).

RESULTS

Effectiveness

The decision-tree model for OS and PFS revealed that serial ^{18}F-FET PET increased the number of correctly identified responders to adjuvant temozolomide chemotherapy compared to MRI alone. With regard to the OS, the proportion of responders additionally identified by ^{18}F-FET PET was 26% higher than by MRI (^{18}F-FET PET responders, 68%; MRI responders based on RANO criteria, 42%). For PFS, the IE of 25% was similar (^{18}F-FET PET responders, 68%; MRI responders based on RANO criteria, 43%). Thus, to identify one responder by ^{18}F-FET PET, four patients had to be examined (number needed to examine, 3.8 for OS; 3.9 for PFS).

Cost Calculation

The ICER resulted in €4,396.83 (OS) and €4,568.90 (PFS) for each responder identified by ^{18}F-FET PET, but not by MRI.

Sensitivity Analyses

The resulting ICER for the chance node intervals of the deterministic sensitivity analysis are presented in Table 1. Figure 2 shows the corresponding Tornado diagrams. The range of ICER values was €2,805.52 - €10,224.32 for OS, and €2,864.73 - €11,205.90 for PFS. Chance nodes N1 and N2 showed by far the most significant impact regarding the minimum and maximum ICER values, as a direct result of their wider variability.

The results of the probabilistic sensitivity analysis showed both a narrow distribution around the mean and a close relation to the calculated IE and ICER values of the decision-tree for OS (mean IE, 26%, CI 24 - 27%; mean ICER, €4,437.41, CI €4,337.24 - €4,919.98) and PFS (mean IE, 25%, CI 23 - 26%; mean ICER, €4,610.24, CI €4,470.05 - €5,119.95), respectively (Table 3, Figure 3). This close relation confirmed the robustness and reliability of the calculated values of the decision-tree.

DISCUSSION

The main finding of the present study is that ^{18}F-FET PET is effective and cost-effective for early identification of responders to adjuvant chemotherapy with temozolomide compared to standard MRI in patients with malignant glioma. Our results are based on the responsiveness to chemotherapy as a surrogate since this responsiveness considerably influences further treatment planning in these patients. This particularly applies to clinically equivocal situations in which treatment-related changes such as pseudoprogression on MRI following chemoradiation with temozolomide might lead to a discontinuation of a benefitting chemotherapy. Thus, a premature and more

aggressive treatment regimen based on the false assumption of non-responsiveness to temozolomide, with the risk of severe side effects, reduced survival, and a decrease in health-related quality of life, can potentially be avoided.

Considering the overall cost of concomitant radiochemotherapy followed by six cycles of temozolomide of approximately €30,000 (*19,20*), the expense for ^{18}F-FET PET for treatment assessment seems to be cost-effective. This particularly applies when considering the total costs for patient care and a potential cost reduction if an unnecessary, more aggressive treatment can be avoided. Thus, a neuroimaging approach combining both conventional MRI and ^{18}F-FET PET has the potential to improve the respective strengths of each imaging modality at acceptable cost.

To the best of our knowledge, this is the first study evaluating the cost-effectiveness of serial ^{18}F-FET PET for assessing response to adjuvant chemotherapy with temozolomide. Recently, a study from Baguet et al. investigated the cost-effectiveness of ^{18}F-FET PET for assessment of treatment response in glioma patients following radiotherapy with concomitant temozolomide (*14*). Similar to our results, the authors found almost equal IE values for PFS and OS and concluded that ^{18}F-FET PET might be cost-effective for that purpose. Nevertheless, there are several differences compared to the present study. In particular, the authors investigated the cost-effectiveness of ^{18}F-FET PET for identifying non-responders to radiotherapy with concomitant temozolomide chemotherapy. Thus, an earlier phase of treatment was analyzed, and the respective decision-trees were based on the clinical assumption of non-responsiveness. Furthermore, the authors investigated ^{18}F-FET PET from the perspective of the Belgian

healthcare system, resulting in different costs for ^{18}F-FET PET. Another difference is the size of the patient samples, which was larger in our study (41 vs. 25 patients).

Other studies evaluated the cost-effectiveness of additional ^{18}F-FET PET compared to MRI alone for biopsy site selection for glioma diagnosis (*12*) and bevacizumab response assessment in patients with progressive malignant glioma (*15*). In analogy to our study, both studies concluded that ^{18}F-FET PET is cost-effective concerning the analyzed clinical scenarios. Compared to our results, the respective ICERs were higher, i.e., €9,114 for one additional correct glioma diagnosis after ^{18}F-FET PET-guided biopsy (*12*), and €8,145 to identify one additional responder to bevacizumab. This difference is due to a lower incremental effectiveness of ^{18}F-FET PET as compared with MRI with regard to Heinzel et al. (*12*). Moreover, while the ICER in the mentioned studies (*12,15*) reflected the cost of adding ^{18}F-FET PET in the diagnostic workup, the ICER in the present study reflects the result of comparing both imaging strategies (^{18}F-FET and MRI) with their respective cost-effectiveness ratios. This limits the meaningfulness of comparing the ICERs of the mentioned studies with the present results. In patients with brain metastases, a further study investigated cost-effectiveness of ^{18}F-FET PET for the differentiation of brain metastases relapse from radiotherapy-induced changes (*18*). The ICER of that study was similar to our results. Taken together, our results confirm previous studies suggesting that ^{18}F-FET PET is cost-effective in the care of patients with brain malignancies.

One limitation of the present study is that the decision-trees for PFS and OS were based on merely one study relying on longitudinal within-group comparisons. Though

these groups comprised a large number of prospectively followed patients, additional studies with prospective designs are warranted, particularly given the paucity of research regarding this crucial medical-economical topic.

In conclusion, this study suggests that ^{18}F-FET PET is cost-effective for early treatment response assessment in glioma patients following chemotherapy with temozolomide and helps to improve patient care at acceptable costs.

FINANCIAL DISCLOSURE

Related to the present work, the authors disclosed no potential conflicts of interest.

KEY POINTS

QUESTION: Is ^{18}F-FET PET cost-effective for early identification of responders to adjuvant chemotherapy with temozolomide in glioma patients?

PERTINENT FINDINGS: Based on published data, ^{18}F-FET PET increased the rate of correctly identified responders by 26% as compared to MRI, resulting in cost of €4,396.83 for each additionally identified responder. This appears to be cost-effective, particularly considering the high cost of temozolomide chemotherapy.

IMPLICATIONS FOR PATIENT CARE: The integration of ^{18}F-FET PET may improve patient care at reasonable cost.

REFERENCES

1. Louis DN, Perry A, Reifenberger G, et al. The 2016 World Health Organization classification of tumors of the central nervous system: a summary. *Acta Neuropathol.* 2016;131:803-820.

2. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med.* 2005;352:987-996.

3. Galldiks N, Dunkl V, Stoffels G, et al. Diagnosis of pseudoprogression in patients with glioblastoma using O-(2-[18F]fluoroethyl)-L-tyrosine PET. *Eur J Nucl Med Mol Imaging.* 2015;42:685-695.

4. Langen KJ, Galldiks N, Hattingen E, Shah NJ. Advances in neuro-oncology imaging. *Nat Rev Neurol.* 2017;13:279-289.

5. Ahluwalia MS, Wen PY. Antiangiogenic therapy for patients with glioblastoma: current challenges in imaging and future directions. *Expert Rev Anticancer Ther.* 2011;11:653-656.

6. Dhermain FG, Hau P, Lanfermann H, Jacobs AH, van den Bent MJ. Advanced MRI and PET imaging for assessment of treatment response in patients with gliomas. *Lancet Neurol.* 2010;9:906-920.

7. Kumar AJ, Leeds NE, Fuller GN, et al. Malignant gliomas: MR imaging spectrum of radiation therapy- and chemotherapy-induced necrosis of the brain after treatment. *Radiology.* 2000;217:377-384.

8. Young RJ, Gupta A, Shah AD, et al. Potential utility of conventional MRI signs in diagnosing pseudoprogression in glioblastoma. *Neurology.* 2011;76:1918-1924.

9. Galldiks N, Law I, Pope WB, Arbizu J, Langen KJ. The use of amino acid PET and conventional MRI for monitoring of brain tumor therapy. *Neuroimage Clin.* 2017;13:386-394.

10. Lohmann P, Elahmadawy MA, Gutsche R, et al. FET PET Radiomics for differentiating pseudoprogression from early tumor progression in glioma patients post-chemoradiation. *Cancers (Basel).* 2020;12:3835.

11. Ceccon G, Lohmann P, Werner JM, et al. Early treatment response assessment using (18)F-FET PET compared to contrast-enhanced MRI in glioma patients following adjuvant temozolomide chemotherapy. *J Nucl Med.* 2021;62:918-925.

12. Heinzel A, Stock S, Langen KJ, Muller D. Cost-effectiveness analysis of FET PET-guided target selection for the diagnosis of gliomas. *Eur J Nucl Med Mol Imaging.* 2012;39:1089-1096.

13. Heinzel A, Stock S, Langen KJ, Muller D. Cost-effectiveness analysis of amino acid PET-guided surgery for supratentorial high-grade gliomas. *J Nucl Med.* 2012;53:552-558.

14. Baguet T, Verhoeven J, De Vos F, Goethals I. Cost-effectiveness of [(18)F] fluoroethyl-L-tyrosine for temozolomide therapy assessment in patients with glioblastoma. *Front Oncol.* 2019;9:814.

15. Heinzel A, Muller D, Langen KJ, et al. The use of O-(2-18F-fluoroethyl)-L-tyrosine PET for treatment management of bevacizumab and irinotecan in patients with recurrent high-grade glioma: a cost-effectiveness analysis. *J Nucl Med.* 2013;54:1217-1222.

16. Wen PY, Macdonald DR, Reardon DA, et al. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. *J Clin Oncol.* 2010;28:1963-1972.

17. Pauleit D, Floeth F, Hamacher K, et al. O-(2-[18F]fluoroethyl)-L-tyrosine PET combined with MRI improves the diagnostic assessment of cerebral gliomas. *Brain.* 2005;128:678-687.

18. Heinzel A, Muller D, Yekta-Michael SS, et al. O-(2-18F-fluoroethyl)-L-tyrosine PET for evaluation of brain metastasis recurrence after radiotherapy: an effectiveness and cost-effectiveness analysis. *Neuro Oncol.* 2017;19:1271-1278.

19. Uyl-de Groot CA, Stupp R, van der Bent M. Cost-effectiveness of temozolomide for the treatment of newly diagnosed glioblastoma multiforme. *Expert Rev Pharmacoecon Outcomes Res.* 2009;9:235-241.

20. Waschke A, Arefian H, Walter J, Hartmann M, Maschmann J, Kalff R. Cost-effectiveness of the long-term use of temozolomide for treating newly diagnosed glioblastoma in Germany. *J Neurooncol.* 2018;138:359-367.

21. R Core Team. A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. 2018.

FIGURES

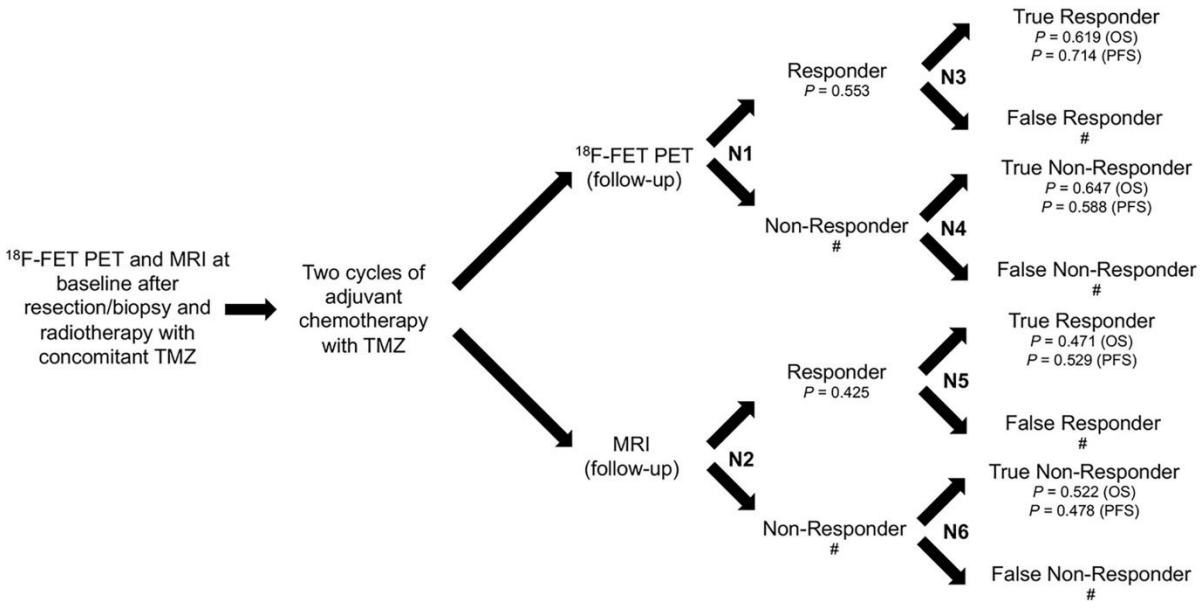

FIGURE 1: Decision-tree model for assessing the effectiveness of ^{18}F-FET PET and MRI to identify a responder to adjuvant chemotherapy with temozolomide based on a PFS ≥ 9 months and an OS ≥ 15 months. Thirty-eight patients underwent serial ^{18}F-FET PET imaging, and 40 patients serial MRI. Nodes N1 and N2 represent chance nodes to be a responder or non-responder according to PET and MRI imaging criteria (i.e., TBR_{max} ≤ or > 0%, and stable disease or progressive disease according to RANO criteria, respectively). Nodes N3-N6 divide each of the four groups of PET and MRI responders (and non-responders) into true and false responders (and non-responders), respectively. **# =** indicates the corresponding likelihood (1-*P*).

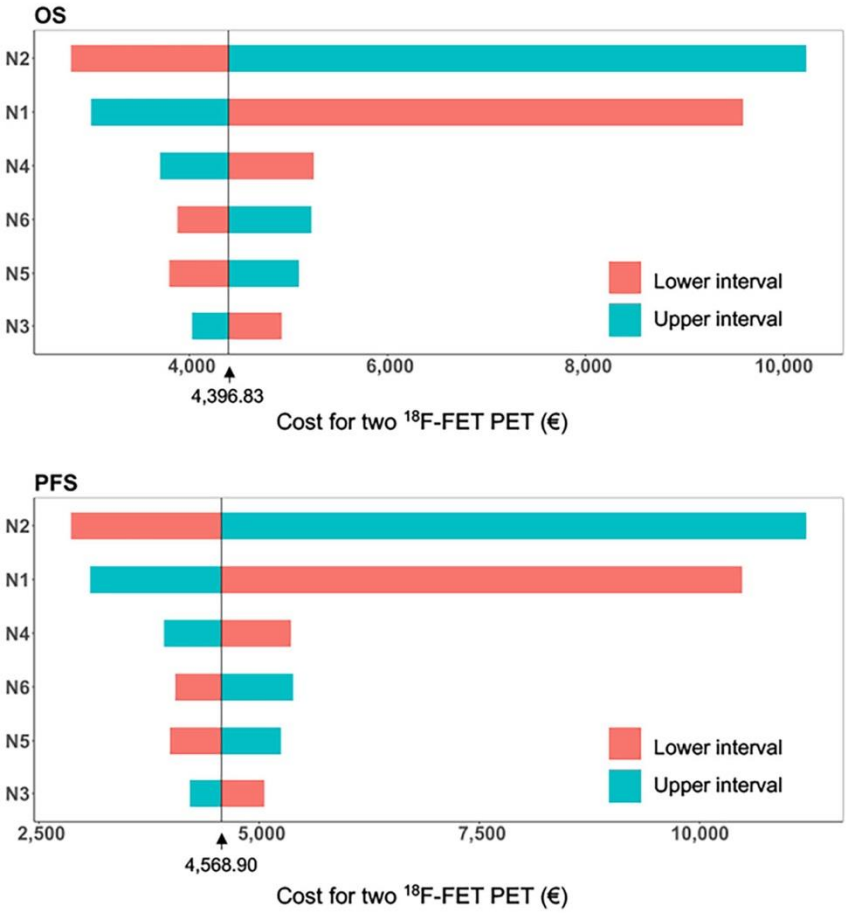

FIGURE 2: Tornado diagram of the incremental cost-effectiveness ratio (ICER) of ^{18}F-FET PET for the identification of a responder to adjuvant chemotherapy with temozolomide based on OS (upper panel) and PFS (lower panel). ICERs were calculated by applying upper and lower interval values, as shown in Table 1, onto change nodes N1-N6.

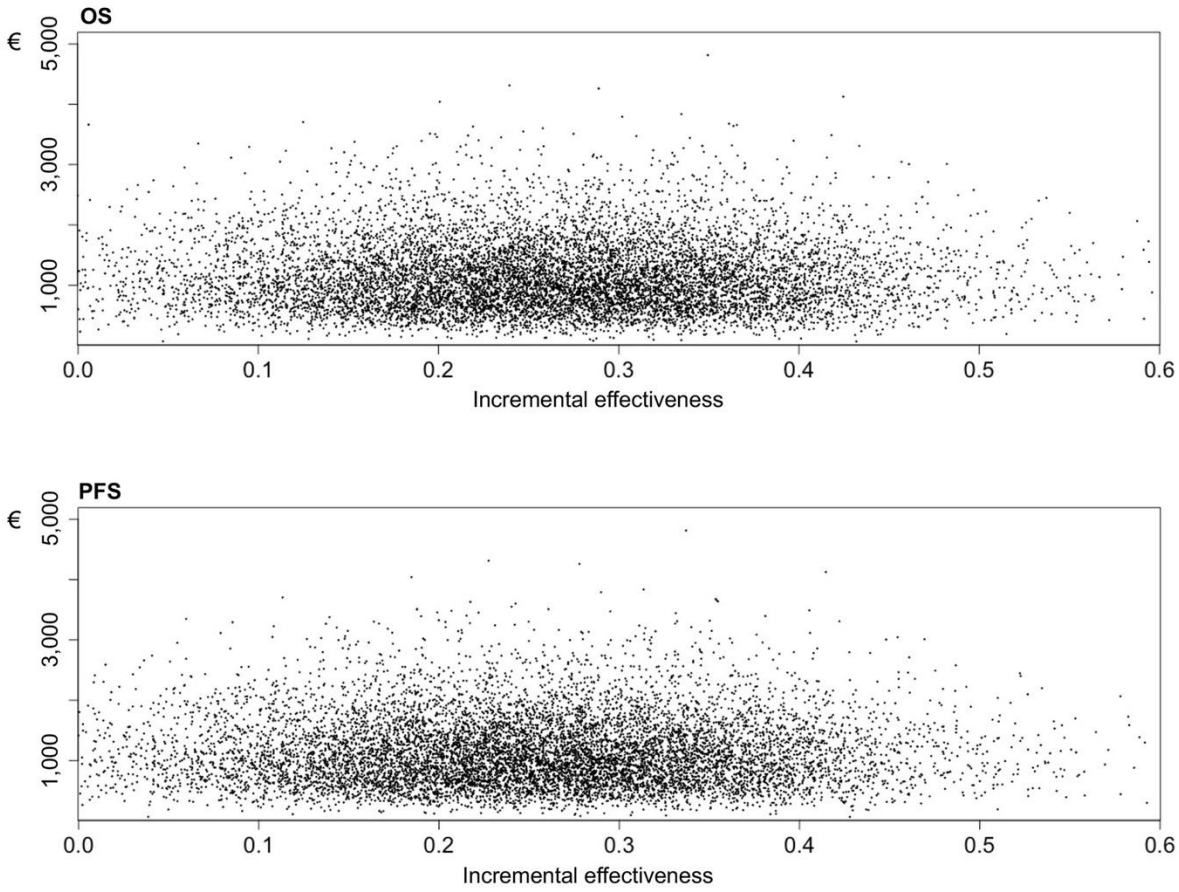

FIGURE 3: Distribution of results from Monte Carlo analysis (dots) about incremental effectiveness of a ^{18}F-FET PET for the identification of one responder to adjuvant chemotherapy with temozolomide compared to MRI based on an OS ≥ 15 months (upper panel) and a PFS ≥ 9 months (lower panel). The x-axis depicts the increase in the likelihood of correct identification of a responder as the outcome (incremental effectiveness). The y-axis depicts the gamma-modulated difference in cost between serial ^{18}F-FET PET and MRI scans. Values with an incremental effectiveness < 0 and > 0.6 are not shown (1% of values).

Table 1: Chance node intervals and corresponding IE and ICER in the one-way deterministic sensitivity analysis for the decision-tree regarding OS and PFS

Chance node	Parameter	Decision-tree OS		Decision-tree PFS	
		lower interval	upper interval	lower interval	upper interval
N1	**Value (%)**	**40.3**	**70.3**	**40.3**	**70.3**
	Resulting IE (%)	12.1	38.5	11.0	37.5
	Resulting ICER (€)	9,586.87	3,008.80	10,477.87	3,083.00
N2	**Value (%)**	**27.5**	**57.5**	**27.5**	**57.5**
	Resulting IE (%)	41.2	11.3	40.4	10.3
	Resulting ICER (€)	2,805.52	10,224.32	2,864.73	11,205.90
N3	**Value (%)**	**54.4**	**69.4**	**63.9**	**78.9**
	Resulting IE (%)	23.5	28.7	22.9	27.5
	Resulting ICER (€)	4,931.75	4,026.92	5,059.04	4,215.10
N4	**Value (%)**	**57.2**	**72.2**	**51.3**	**66.3**
	Resulting IE (%)	22.0	31.2	21.6	29.5
	Resulting ICER (€)	5,256.23	3,704.08	5,359.32	3,919.68
N5	**Value (%)**	**39.6**	**54.6**	**45.4**	**60.4**
	Resulting IE (%)	30.5	22.7	29.0	22.1
	Resulting ICER (€)	3,796.09	5,102.79	3,987.34	5,246.52
N6	**Value (%)**	**44.7**	**59.7**	**40.3**	**55.3**
	Resulting IE (%)	29.8	22.1	28.6	21.5
	Resulting ICER (€)	3,880.10	5,232.88	4,048.80	5,384.38

Abbreviations: ICER = incremental cost-effectiveness ratio; **IE =** incremental effectiveness; **OS =** overall survival; **PFS =** progression-free survival

Table 2: Input variables used in the Monte Carlo analysis

Chance node	Calculated value (OS, %)	Calculated value (PFS, %)	SD (%)
N1	55.3	55.3	7.5
N2	42.5	42.5	7.5
N3	61.9	71.4	3.75
N4	64.7	58.8	3.75
N5	47.1	52.9	3.75
N6	52.2	47.8	3.75

Calculated values for chance nodes were taken from the decision-tree for OS and PFS, respectively. Standard deviations were set according to the confidence intervals of the deterministic sensitivity analysis, similar to Baguet et al. (*14*). **Abbreviations: OS =** overall survival; **PFS =** progression-free survival; **SD =** standard deviation

Table 3: Statistics resulting from the Monte Carlo analysis (10,000 samples) for the effectiveness of ^{18}F-FET PET and MRI for identification of a responder to adjuvant chemotherapy with temozolomide

Value/ Percentile	OS			PFS			Difference in cost PET - MRI (€)
	MRI (%)	PET (%)	IE (%)	MRI (%)	PET (%)	IE (%)	
Mean	42.1	68.2	26.1	42.9	68.0	25.1	1138.87
SD	7.9	7.1		7.8	7.0		570.98
Minimum	13.6	35.2	21.6	14.1	34.6	20.5	65.74
2.5%	26.7	53.4	26.7	27.5	53.4	25.9	328.05
10%	32.0	58.7	26.7	32.8	58.6	25.8	502.97
Median	42.1	68.5	26.4	42.9	68.3	25.4	1037.76
90%	52.3	77.0	24.7	53.0	76.6	23.7	1908.62
97.5%	57.7	81.2	23.5	58.2	80.8	22.6	2507.42
Maximum	71.4	89.0	17.6	71.7	88.6	16.9	4813.26

The left and middle columns indicate the probability of correctly detecting a responder to adjuvant temozolomide chemotherapy concerning OS and PFS by MRI or PET, respectively. Column IE indicates their difference and thus the incremental effectiveness in using ^{18}F-FET PET to identify a responder. The right column indicates the gamma-distributed difference in cost between serial ^{18}F-FET PET and MRI scans. **Abbreviations: IE =** incremental effectiveness; **MRI =** magnetic resonance imaging; **OS =** overall survival; **PET =** positron emission tomography; **PFS =** progression-free survival; **SD =** standard deviation

Graphical Abstract